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Age of onset, clinical characteristics, and 15-year course of anxiety disorders in a prospective, longitudinal, observational study

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Abstract

Background—Age of onset is rarely studied in the anxiety disorders literature. The current study examined age of onset as it relates to clinical characteristics and course of anxiety disorders using a prospective, longitudinal, observational design.

Methods—Fifteen-year follow-up data were examined for participants with panic disorder with (PDA) or without (PD) agoraphobia, social phobia (SP), and/or generalized anxiety disorder (GAD) at baseline. Logistic regression analyses were conducted to determine whether age of onset was associated with demographic or clinical variables at baseline. Cox regression analyses were conducted to examine longitudinal course (time to recurrence and recovery, respectively) for each diagnostic group.

Results—At baseline, PD participants with early onset (i.e., < age 20) were more likely to have comorbid MDD, GAD, and SP relative to late-onset participants ($\geq$ age 20). For PDA, early-onset participants were less likely to be married, and more likely to have both GAD and SP at baseline. With respect to longitudinal course, earlier onset was associated with an increased likelihood of recurrence in participants with PDA. No other models reached significance.

Limitations—The sample sizes for some disorders were comparatively small in relation to PDA, and all participants were treatment-seeking, which may limit generalizability.

Conclusions—For some anxiety disorders, earlier age of onset appears to be associated with greater severity and worse course, as evidenced by increased risk of recurrence over 15 years of follow-up. Early interventions focused on children and adolescents may alleviate some of the public health burden associated with anxiety disorders.

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Contributors

Dr. Keller designed the larger study on which the current manuscript is based and wrote the protocol. Dr. Ramsawh developed the current study concept, managed the literature searches, and wrote the first draft of the manuscript. Ms. Dyck conducted and Dr. Stout supervised the statistical analyses. Dr. Weisberg provided significant input on all drafts of the manuscript. All authors contributed to and have approved the final manuscript.

Keywords

Anxiety disorders; Panic Disorder; Phobic disorders; Longitudinal studies; Prospective studies

Introduction

Anxiety disorders are the most prevalent group of psychiatric disorders in the United States, with more than one out of every four Americans meeting lifetime criteria for an anxiety disorder (Kessler et al. 2005). Associated medical expenditures, lost productivity, and functional impairment are estimated at \$42.3–\$46.6 billion annually (Dupont et al., 1996; Stein et al., 2005; Greenberg et al., 1999; Rice and Miller, 1998). Anxiety disorders are also among the earliest psychiatric conditions to manifest, with a median age of onset of 11 years (Kessler et al. 2005). As such, prevalence rates in individuals under 18 are estimated to be 5.7–12.8%, making anxiety disorders more prevalent in children than either mood disorders or attention deficit hyperactivity disorder (Angold et al. 2002; Costello et al. 1997; Costello et al. 2003; Fergusson et al. 1993; Lewinsohn et al. 1998; Shaffer et al. 1996). Even when treated, anxiety disorders tend to have a chronic and unremitting course of illness (Bruce et al. 2005; Ramsawh et al. 2009).

Despite having important implications for research and clinical practice, age of onset is rarely studied in the anxiety disorders literature. Several studies have found that early-onset anxiety disorders are associated with greater severity (Campbell et al. 2003; Dalrymple et al. 2007), more comorbidity (Campbell et al., 2003; Goodwin and Hamilton 2002; Iketani et al., 2004), and greater familial loading (Goldstein et al., 1997; Segui et al., 1999; Venturello et al., 2002) for anxiety disorders.

What is unclear is whether age of onset affects course of anxiety disorders. Based on the existing literature, one hypothesis is that onset early in life is a marker for a more severe course of illness. However, a competing hypothesis is that earlier age of onset results in a less severe course of illness—perhaps due to earlier entrée into treatment, or more time for regression to the mean. In previous research we found that older adults had a less severe course over time (Ramsawh et al., 2009); however, we did not test whether age of onset influenced the trajectory of their illness. Both hypotheses (i.e., that early age of onset will be associated with more severe or less severe course) were tested in the current study. We examined baseline demographic and clinical characteristics in relation to age of onset, and the association of course and age of onset. With its prospective, observational, longitudinal design; comprehensive diagnostic interviews; and over 15 years of follow-up data collected, the Harvard-Brown Anxiety Research Project (HARP) is uniquely positioned to examine age of onset as it relates to longitudinal course of anxiety disorders.

Methods

Participants

Fifteen-year follow-up data were examined for HARP participants. The original sample consisting of 711 participants with a past or current diagnosis of panic disorder with (PDA) or without (PD) agoraphobia, social phobia (SP), and/or generalized anxiety disorder (GAD) at baseline. Most comorbid diagnoses were allowed, with exceptions including the presence of an organic brain disorder or a history of schizophrenia, or current psychosis at intake. This sample was recruited in 1989–1991 from 11 different mental health outpatient clinics around New England; these methods are described in more detail elsewhere (Massion et al., 1993). Participants were 18 or older, were willing to participate, and gave written informed consent.

Participants were included in the current analyses if they had completed at least three follow-up interviews. This resulted in 71 participants with PDA, 49 participants with SP, 45 participants with GAD, and 20 participants with PD being excluded from the final sample. A total of 581 participants had sufficient follow-up data to be included in the current analyses (diagnostic groups were not mutually exclusive).

Diagnostic assessment

Participants were interviewed at intake using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R Non-Affective Disorders–Patient Version (SCID-P) (Spitzer et al., 1988) and the Research Diagnostic Criteria (RDC) Schedule for Affective Disorders-Lifetime (SADS-L; Endicott & Spitzer, 1978). Items from these measures were combined to create the SCALUP, a structured interview used to assess intake diagnoses.

Following intake, current anxiety and other Axis I disorder severity, along with social, interpersonal, and occupational functioning, were assessed prospectively at 6- to 12-month intervals, with assessments every 6 months for the first two years of the study, annually for years 3–6, every 6 months for years 7–13, and annually thereafter. The Longitudinal Interval Follow-up Evaluation (LIFE) (Keller et al., 1987) was used during follow-up interviews to assess the weekly course of Axis I disorders. Ratings for each diagnosis were made by trained bachelor's or master's level clinicians using *psychiatric status ratings* (PSRs) from 1 to 6, with higher ratings reflecting greater impairment and more diagnostic criteria being met. A PSR of 1 indicates that no symptoms and no impairment are present, while a PSR of a 6 indicates that DSM-III-R criteria are met along with severe impairment related to the diagnosis in question. The study design also contains retrospective elements, in that age of onset was determined via participant recall. Additionally, PSRs were assigned for each week since the last follow-up based on the participant's detailed recall of his or her symptoms over this interval. The LIFE has been found to have good to excellent inter-rater reliability, test-retest reliability, and concurrent and discriminant validity when administered by trained bachelor's or master's level clinicians (Warshaw et al., 1994; Warshaw et al., 2001).

Analytic approach

Statistical analyses were conducted with SAS Version 9.2 (SAS Institute, Cary, N.C.). First, adjusting for age at baseline, logistic regression analyses were conducted to determine whether age of onset was associated with demographic or clinical variables at baseline including gender, education, marital status, and Axis I disorder comorbidity. "Early onset" was defined as age of onset < 20; "late onset" was defined as ≥ 20 . This operational definition is in accordance with other investigators who have defined adult onset or late onset per a cutoff of age 18, 20, or 25 (Campbell et al 2003; Goldstein et al. 1997; Iketani et al. 2004; Segui et al. 1999; Venturello et al. 2002). To examine the association between age of onset and longitudinal course, Cox regression analyses were conducted to examine course over the first 15 years of the study—time to recurrence and time to recovery, respectively—for each diagnostic group. *Recurrence* was defined as a PSR of 5 or greater for four consecutive weeks following a recovery. *Recovery* was defined as eight consecutive weeks at psychiatric status ratings of 2 or less. For PDA, recurrence and recovery definitions needed to be met for both panic disorder and agoraphobia symptoms. For course analyses, age of onset was treated as a continuous variable. Covariates included gender, Hollingshead rating, education, marital status, global assessment of functioning (GAF) score, and comorbidity (number of comorbid Axis I disorders) at baseline.

Results

Age of onset and baseline demographic and clinical data (Table 1)

At baseline, PD participants with early onset were more likely to have comorbid MDD (OR = 3.556, CI = 1.292 – 9.791, $p = .0141$), GAD (OR = 8.578, CI = 2.394 – 30.738, $p = .0028$), and SP (OR = 4.240, CI = 1.258 – 14.285, $p = .0259$) relative to late-onset participants. For PDA, early-onset participants were less likely to be married (OR = 0.628, CI = 0.409 – 0.966, $p = 0.0349$), and more likely to have both GAD (OR = 1.991, CI = 1.175 – 3.373, $p = 0.0105$) and SP (OR = 2.255, $p = 0.0049$) at baseline.

Age of onset and longitudinal course

For PDA, age of onset was significantly and inversely associated with likelihood of recurrence ($\chi^2 = 5.3548$, $p = 0.0207$). That is, earlier age of onset was associated with increased likelihood of recurrence after a period of remission. No other models reached significance.

Discussion

The primary aim of the current study was to examine the relationship between age of onset and course of anxiety disorders. Baseline demographic and clinical differences associated with early vs. late age of onset were also examined. In addition to baseline differences suggesting increased severity in early-onset illness, the current findings suggest that early onset is also associated with worse course, at least for certain anxiety disorders. Investigators have noted the almost complete absence of psychiatric studies examining age of onset in relation to either clinical correlates or course of illness (Kessler & Wang, 2008), and the few published studies of age of onset in anxiety disorders are largely cross-sectional in nature. In this context, the current findings represent a novel contribution to the literature in this neglected area. Other strengths of the current study include the 15-year follow-up period; the prospective, observational design; and the use of full diagnostic interviews to assess the presence of anxiety and other psychiatric conditions.

Several early-onset disorders seemed to be characterized by increased severity at baseline. Specifically, individuals with early-onset PD were more likely to have comorbid MDD, GAD, and SP at baseline. Individuals with early-onset PDA were less likely to be married, and more likely to have comorbid GAD and SP at baseline. These findings are in accordance with previous research suggesting increased comorbidity associated with early-onset anxiety disorders (Campbell et al., 2003; Goodwin and Hamilton, 2002; Iketani et al., 2004).

We also found support for an association between age of onset and longitudinal course of anxiety disorders. This is the first study to our knowledge that has examined this association empirically. Over 15 years of follow-up, individuals with PDA were more likely to have a recurrence of illness after periods of recovery. Findings for the other disorders failed to reach significance. One possible explanation for this has to do with differences in age of onset for each of the anxiety disorders examined here. While GAD and SP during childhood and adolescence is not uncommon, PD with or without agoraphobia usually onsets in early adulthood; earlier onsets are relatively rare in comparison (Kessler et al. 2005). Thus, perhaps early onset of PDA signals a particularly pernicious form of this illness. However, it is also possible that the analyses for some disorders may have been underpowered. Significant findings may have emerged for PDA alone because the sample size was much larger compared to those for the other disorders (see Table 1). Future investigation will be necessary to examine the specificity of the current age of onset findings with regard to diagnosis.

There are several other limitations worth noting. First, there are limitations to generalizability--the current sample was treatment-seeking at baseline, and participants were only included in the current analysis if they completed at least three follow-up interviews. Thus, the sample may not fully represent individuals with anxiety disorders in the general population. Second, the current sample was enrolled in 1989–1991 and therefore there may be cohort effects (i.e., differences in the prevalence of anxiety disorders among different birth cohorts). Third, while the current study attempts to minimize the well-known limitations of retrospective report through the use of a follow-up design that re-evaluates participants at relatively short intervals (i.e., every 6 to 12 months over the 15-year follow-up period), this does not entirely “fix” the problem of memory bias in reporting age of onset of illness. Fourth, for purposes of comparison, we chose to examine age of onset using a common cutpoint of age 20 for all diagnoses in analyses involving baseline demographic and clinical characteristics. Other investigators who define “early onset” and “late onset” differently may obtain different results. In addition, future studies should explore whether using different cutpoints for different anxiety disorders (e.g., median age of onset for each disorder) may be more meaningful. Finally, it is worth noting that the current study did not attempt to disentangle the possible overlapping effects of age of onset and duration of illness. That is to say, it is unclear whether individuals with early-onset PDA have a worse course primarily because of factors related to having an onset of illness early in life, or whether their worse prognosis is due to simply having the illness for a longer period of time relative to individuals with a later onset. We considered examining length of illness as a covariate in the current analysis but found that multicollinearity with age of onset precluded this. Investigators should consider ways in which effects of age of onset and length of illness might be disentangled in future studies—for example, by examining clinical presentation and course in individuals who have had an equivalent length of illness, but who differ by age of onset (e.g., adult vs. childhood onset). A final future direction involves determining mediators and moderators of the relationship between age of onset and course—for example, genetic risk factors and first entrée into treatment each represent two potentially interesting areas of inquiry.

In conclusion, the current findings suggest that at least for some anxiety disorders, earlier age of onset appears to be associated with greater severity and worse course, as evidenced by increased risk of recurrence over 15 years of follow-up. This provides further support for the deleterious effects of early onset of psychiatric illness. Greater focus on prevention and intervention efforts may assist in alleviating a large part of the public health burden associated with anxiety disorders.

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Table 1

Baseline demographic and clinical characteristics by age of onset.

Variable	SP				PDA		GAD	
	(N = 176)				(N = 357)		(N = 179)	
Onset Late	Early	Late	Early	Late	Early	Late	Early	Early
	(n = 20)	(n = 44)	(n = 138)	(n = 159)	(n = 88)			
(n = 55)	(n = 110)	(n = 26)						
Female (%)	70.0	56.8	69.6	70.4				73.9
70.9	60.0	50.0						
Age (S.D.)	36.9 (9.5)	41.6 (11.8)	39.2 (12.5)	41.9 (11.3)				37.4 (10.2)
44.8 (12.9)	39.3 (11.3)	43.7 (9.1)						
At least some college	35.0	45.5	29.9	39.6				40.2
30.9	35.8	34.6						
(%)								
Married (%)	50.0	50.0	47.1 *	62.9 *				48.9
58.2	45.5	65.4						
GAF (S.D.)	56.5 (11.4)	63.0 (11.5)	59.7 (10.4)	60.5 (10.3)				57.5 (10.9)
56.0 (11.0)	56.4 (10.1)	56.9 (11.9)						
MDD (%)	45.0 *	22.7 *	23.9	20.1				36.4
38.2	36.4	23.1						
GAD (%)	40.0 *	9.1 *	26.1 *	15.7 *				-----
-----	35.5	30.8						
SP (%)	30.0 *	9.1 *	21.7 *	12.0 *				31.8
34.6	-----	-----						
PD (%)	-----	-----	-----	-----				8.0
9.1	7.3	7.7						
PDA (%)	-----	-----	-----	-----				44.3
40.0	36.4	34.6						

Variable	SP		PD		PDA		GAD	
	Early	Late	Early	Late	Early	Late	Early	Late
Onset	(N = 176)		(N = 82)		(N = 357)		(N = 179)	
	Early	Late	Early	Late	Early	Late	Early	Late
	(n = 20)	(n = 44)	(n = 138)	(n = 159)	(n = 88)			
	(n = 55)	(n = 110)	(n = 26)					
Years with diagnosis	23.6 (12.2)	5.7 (6.3)	27.0 (13.2)	11.7 (9.3)	27.6 (10.7)			
11.6 (11.7)	28.8 (12.1)	17.1 (9.5)						
(S.D.)								
# of follow-up	9.6 (4.3)	9.5 (3.8)	10.3 (4.2)	10.3 (4.2)	10.6 (4.2)			
9.5 (4.2)	9.8 (4.4)	10.5 (4.5)						
interviews (S.D.)								

PD = Panic disorder; PDA = Panic disorder with agoraphobia; GAD = Generalized anxiety disorder; SP = Social phobia; MDD = Major depressive disorder; GAF = Global assessment of functioning.

* p < .05